It is believed that no fee is due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to this document, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski Account L.L.P. No.: 50-1212/INRP:050.

Reconsideration of the application in view of the following amendments and remarks is respectfully requested.

I. AMENDMENT

Please make the following amendments:

In the Claims:

Please amend claim 1 and claim 32 as follows:

1. (Amended four times) A method of reducing the growth rate of a tumor, comprising contacting a cell within said tumor with (a) a DNA segment encoding a functional p53 protein and (b) a DNA damaging agent in a combined amount effective to inhibit the growth of said tumor.

~~32~~ 25. (Amended three times) A composition comprising a) an exogenous DNA segment encoding a functional p53 polypeptide and b) compound comprising a DNA damaging agent.

A copy of the marked-up version of claims indicating the amendments can be found in Appendix A. A clean copy of pending claims as they will exist if the Amendment is entered can be found in Appendix B.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-10, 12-20, 22-26, 32-37, 39-61, 77-79, 83-91, 96-101, 111, 112, 116-120, and 128-130 were pending prior to the Office Action dated July 3, 2002. Claim 1 and claim 32 have been amended to clarify the claims and place them in better condition for allowance or appeal.

B. Rejections Under 35 U.S.C. §112, Second Paragraph

The Action has rejected claims 1-10, 12-20, 22-26, 46-61, 77-79, 83-91, 96-101, 111, 112, 116-120, and 128-130, under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner has questioned if the term "functional p53 protein" that occurs in line 4 of claim 1 is the same as the "functional p53 protein" described in line 2.

Applicants present amended claim 1 to render this issue moot. The phrase "in a combined amount effective to inhibit growth of said tumor" in amended claim 1 describes the therapeutic method in sufficient detail. Contrary to the Examiner's contention, no other limitations or elements are required in this claim. A person of skill in the art, on reviewing the claims in light of the specification, knows what steps to perform to achieve the claimed method. No more is needed under 35 U.S.C. §112, second paragraph. Therefore, Applicants request the withdrawal of the 35 U.S.C. §112, second paragraph, rejections to claims 1-10, 12-20, 22-26, 46-61, 77-79, 83-91, 96-101, 111, 112, 116-120, and 128-130.

C. Rejections Under 35 U.S.C. §103(a)

The Action issues several obviousness rejections against the claims, which are all defective. Each rejection raised in the Action is individually addressed below. Applicants also

present amended claim 32 to clarify this claim further. In addition, Applicants present a Decision by the Board of Patent Appeals and Interferences (Board), submitted herewith as Appendix C, that was issued in an unrelated case with similar technology. The Decision reflects the Board's opinion that the art at the time of the filing of this application in fact teaches away from the combination of "exogenous p53" and "a DNA-damaging agent".

1. Rejection of claims 32-35 over Kuerbitz *et al.*, in view of Fritsche *et al.*

The Examiner has rejected composition claims 32-35, under 35 U.S.C. §103(a), alleging that Kuerbitz *et al.* (Kuerbitz) teaches a composition comprising an exogenous DNA segment encoding a functional p53 polypeptide and a DNA damaging agent and that Fritsche *et al.* (Fritsche) teaches a composition comprising a gene encoding a functional p53 polypeptide in combination with a DNA damaging agent and lists numerous DNA damaging agents listed in claim 33.

Applicants respectfully traverse. When applying a 35 U.S.C. §103(a) rejection, the following tenets of patent law must be adhered to make a *prima facie* case of obviousness:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be **some suggestion or motivation**, either **in the references themselves** or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or **references when combined) must teach or suggest all the claim limitations**.
>
> The **teaching or suggestion** to make the claimed combination and the reasonable expectation of success **must both be found in the prior art, not in applicant's disclosure**. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). (emphasis added)
>
> M.P.E.P. § 2143

The references cited in the Action do not satisfy the first requirement. There is no suggestion or motivation to combine the references to create the claimed composition.

The Kuerbitz reference shows merely that wt-p53 is expressed after DNA-damage by γ–irradiation (XRT) in non-hematopoietic mammalian cells and that the endogenous p53 status of a cell regulates the progress or arrest of a cell into the cell cycle following DNA-damage by radiation (see page 7491, column 2, third paragraph; and section entitled "Results" on pages 7492-7494, of Kuerbitz). The data in Kuerbitz indicates that expression of wildtype p53, following XRT arrests cell cycle in cells that are in the G1-phase (see page 7492, second column, of Kuerbitz). The Examiner has cited the materials and methods section and figure 4 of Kuerbitz in the Action as allegedly teaching the composition of the invention. First, Applicants dispute that Kuerbitz teaches a composition comprising "exogenous p53" and "**a compound comprising a DNA-damaging agent**." Kuerbitz teaches **irradiation** which cannot be comprised in a compound. Thus, Applicants contend that Kuerbitz does not teach the instant compositions. Also, Applicants would like to note that the experiments described in these cited sections, which describe the transfection of cells using p53 encoding plasmid vectors, are to analyze the effects of DNA-damage by irradiation on the p53 status of a cell. The experiments in Kuerbitz are aimed at studying the p53 status after irradiation related DNA-damage in a cell and are not intended as a composition per say for any therapeutic utility. Furthermore, Kuerbitz does not discuss or suggest any cancer treatment or the use of an *exogenous* DNA segment encoding a functional p53 polypeptide in combination with compounds that are DNA damaging agents. Moreover, there is no reason provided in Kuerbitz that motivates or suggests combining a DNA-damaging agent such as those described in Fritsche with exogenous p53.

The article by Fritsche is cited by the Action as providing "a DNA damaging agent." Fritsche describes the accumulation of endogenous p53 by DNA damaging agents and shows that the accumulation of p53 is due to increased protein stability and **not** enhanced gene expression. Although several DNA-damaging agents have been described in Fritsche, **the desirability to combine these agents** with an *exogenous* p53 **has not even been suggested.** Furthermore, Fritsche does not discuss or suggest any cancer treatments or the use of an *exogenous* DNA segment encoding a functional p53 polypeptide in combination with these agents.

None of the cited references **teach the desirability** to use "exogenous p53" and "compound comprising a DNA-damaging agent" as therapeutic agents for cancer. Further, neither of the references **suggest administering** *exogenous* p53 to cancer cells in combination with a DNA-damaging compound. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01 citing *In re Mills,* 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990) (emphasis added). In this case, the cited references do not suggest that they should be combined with one another. Instead, the Examiner is seeking to **employ impermissible hindsight** in reconstructing the elements necessary to achieve the invention piecemeal from the prior art. *See Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 873 (Fed.Cir.1985). The Federal Circuit has repeatedly held that such hindsight reconstruction is an improper basis for a §103 rejection. *See id.* In view of the above, Applicants request withdrawing the rejections based on Kuerbitz and Fritsche.

In addition, Applicants also present evidence in the form of a Decision by the Board of Patent Appeals and Interferences that was issued in an unrelated application, U.S. Serial No.

08/335,461 (the '461 application), submitted herewith as Appendix C. The claimed technology in the '461 application involves "a method for increasing the therapeutic effect of a cancer therapy comprising delivering a wild-type p53 gene to a tumor cell which is deficient in its wild type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and subjecting said tumor cell to said cancer therapy." The cancer therapies include the use of chemotherapeutic agents (dependent claim 5 of the '461 application). The Examiner had rejected claims in the '461 application under 35. U.S. C. §103. The Board reversed the Examiner's rejections based on the evidence presented by the Appellants, particularly Vogelstein (Vogelstein *et al.*, *Cell*, 70, 523-526, 1992), attached herewith as Appendix D. Vogelstein indicates that the absence of wild-type p53, represented by p53 mutations, in fact increases sensitivity to antitumor agents (page 9, last paragraph, Appendix C). In reversing the Examiner's rejections the Decision states:

> "Thus, Appellants have provided evidence which would reasonably suggest that **one of ordinary skill** in this art at the time of the invention would have expected that the likely result of combining [p53 therapies cited in art] with other types of cancer therapies described by [another prior art reference] would have been that the **transformed tumor cells would have been more resistant to such cancer therapies**." (Emphasis added) (page 10, last paragraph, Appendix C).

In relation to the present invention, Vogelstein, which is a pre-filing publication, teachs a person of skill in the art that the present compositions of "exogenous p53" and "a compound comprising a DNA-damaging agent" would in fact render a cell **more resistant** to the DNA-damaging agent. Thus, the compositions of the present invention would be far from desirable, and hence not at all an obvious choice for a skilled artisan. Applicants therefore request withdrawal of the rejections to the composition claims.

2. Rejection of claims 32-37 and 39-41 over Kuerbitz *et al.* with Fritsche *et al.* and further in view of Bacchetti *et al.*

The Examiner has rejected claims 32-37 and 39-41 over Kuerbitz and Fritsche, further in view of Bacchetti *et al.* (Bacchetti), alleging that although Kuerbitz and Fritsche do not describe adenoviral vectors expressing p53, Bacchetti allegedly teaches the use of adenoviral vectors expressing p53. The Examiner alleges that it would be obvious to combine the teachings of Kuerbitz and Fritsche with those of Bacchetti. The Action also alleges that one would be motivated to combine the references as Bacchetti allegedly teaches advantages and desirability to use adenoviral vectors. Finally, the Action contends that a person of skill in art would have a reasonable expectation of success upon combining the cited art.

Applicants respectfully traverse. For the reasons discussed in the previous section, the references of Kuerbitz and Fritsche do not render claims 32-37 and 39-41 obvious. The addition of Bacchetti does nothing to address the defect in the combination of references. Bacchetti is cited as teaching only the advantageous and desirable use of an adenoviral vector. It does not remedy the lack of suggestion or desirability in Kuerbitz and Fritsche to combine "exogenous p53" with "compound comprising a DNA-damaging agent" to reach at the compositions of the invention. Thus, claims 32-37 and 39-41 are not rendered obvious by the cited references. Applicants respectfully request this rejection be withdrawn.

3. Rejection of claims 32-37 and 39-44 over Kuerbitz *et al.* and Fritsche *et al.* with Bacchetti *et al.* further in view of the Stratagene Catalog

The Examiner alleges that Kuerbitz, Fritsche and Bacchetti together teach the compositions of the invention and that the Stratagene Catalog allegedly teaches kits. Therefore,

the Examiner alleges that it is *prima facie* obvious to one of skill in the art to combine the teachings of the cited art with the Stratagene Catalog that allegedly describes the advantages of a kit.

Applicants respectfully traverse. Again, for the reasons discussed above, the claimed invention is not rendered obvious by the combination of Kuerbitz, Fritsche and Bacchetti. The addition of the Stratagene catalog does not address the fundamental defect with the obviousness rejection of claims from which the kit claims depend. For this reason alone, the obviousness rejection fails.

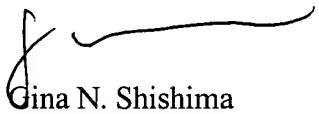
Applicants further contend that, there is simply no motivation or suggestion to combine *any* of the previously cited references with the Stratagene catalog. The Stratagene catalog does **not** provide even a single kit involving a pharmaceutical composition for use in treating disease. Instead, it concerns reagents and kits for scientific experiments such as DNA and RNA Sequencing Kits, Exo/Mung Nuclease Detection Kit, RNA Transcription Kit, RNA Transcription Buffer Kit, mRNA Capping Kit, *In vitro* Express Translation Kit, and *pico*Blue Immunoscreening Kit. None of these kits are intended for use as a treatment or pharmaceutical composition. This reference simply does not concern the type of kits contemplated by the claimed invention. As such, it does not suggest or motivate a person of ordinary skill in the art to combine the cited references to produce the claimed invention. A *prima facie* case of obviousness requires at least this much. Thus, Applicants respectfully request this rejection be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn because they are in condition for allowance. At the very least, Applicants request entry of these amendments in order to place the case in better form for an appeal.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,



Gina N. Shishima
Reg. No. 45,104
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

Date: September 3, 2002